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(54) Title: TETRAHYDROPYRIDINO OR PIPERIDINO HETEROCYCLIC DERIVATIVES

(57) Abstract: A tetrahydropyridino or piperidino heterocyclic derivative represented by the formula [I]: A-Het [I] has a high affinity for CRF receptors and is effective against diseases in which CRF is considered to be involved.

DESCRIPTION

TETRAHYDROPYRIDINO OR PIPERIDINO HETEROCYCLIC
DERIVATIVES

TECHNICAL FIELD

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, 5 such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, 10 immunity-related diseases, alopecia, etc.

BACKGROUND ART

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a 15 core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995). For CRF, there are the following two paths: a path by which CRF acts on peripheral immune system or 20 sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in central nervous

system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like 5 symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in 10 central nervous system.

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, 15 Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, 20 cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, 25 antagonists against CRF receptors are useful as therapeutic agents for the diseases described above.

An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for

diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug-dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, etc.

DISCLOSURE OF THE INVENTION

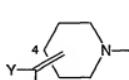
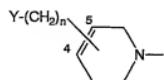
The present inventors earnestly investigated 10 tetrahydropyridino or piperidino heterocyclic derivatives and consequently found novel tetrahydropyridino or piperidino heterocyclic derivatives having a high affinity for CRF receptors, whereby the present invention has been accomplished.

15 The present invention is explained below.

The present invention is a tetrahydropyridino or piperidino heterocyclic derivative represented by the following formula [I]:

A-Het [I]

20 wherein A is a group represented by the following formula [III] or [IV]:



wherein the position of substitution by the $Y-(CH_2)_n-$ group of the group represented by the formula [III] is 4-position or 5-position, the position of substitution by the $Y-C(R^0)=$ group of the group represented by the formula [III] is 3-position or 4-position,

R^0 is a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group or a C_{3-8} cycloalkyl- C_{1-5} alkyl group,

n is an integer of 0 to 5, and

Y is a cyano group, a group represented by

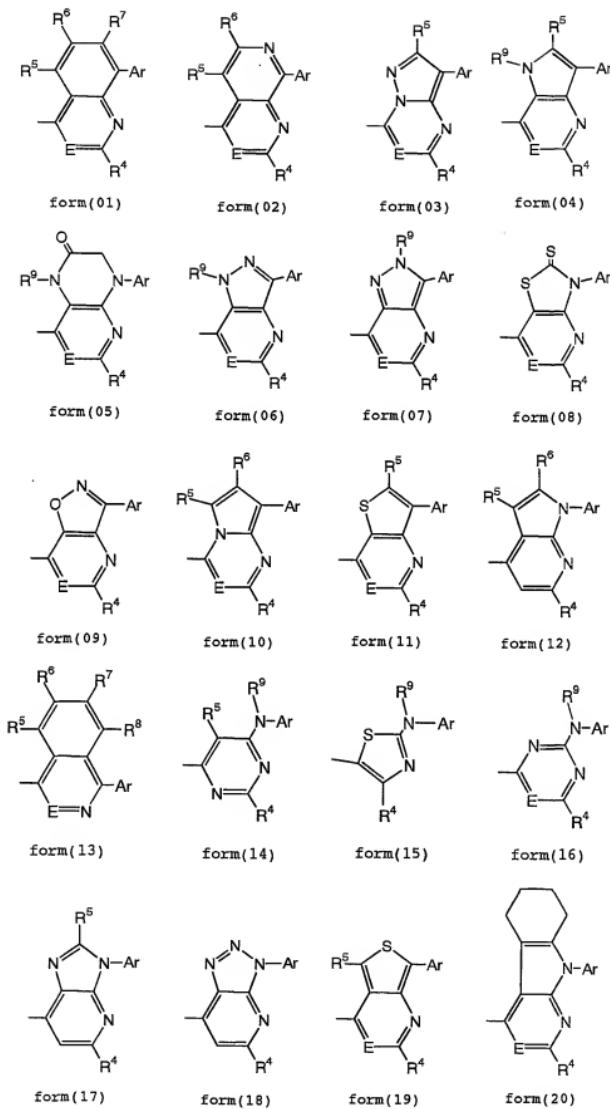
the formula $-CONR^1(R^2)$ (wherein each of R^1 and R^2 , which may be the same or different, is a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyl- C_{1-5} alkyl group, a C_{1-5} alkoxy- C_{1-5} alkyl group, a C_{3-8} cycloalkyloxy- C_{1-5} alkyl group or a phenyl group, or R^1 and R^2 , when taken together with the adjacent nitrogen atom, represent a 5- to 8-membered saturated heterocyclic group represented by the formula:



(wherein B is CH_2 , NH , $N-C_{1-5}$ alkyl, $N-C_{3-8}$ cycloalkyl, $N-C_{1-5}$ alkyl- C_{3-8} cycloalkyl, O or S) or a group

represented by the formula $-CO_2R^3$ (wherein R^3 is a hydrogen atom, a C_{1-5} alkyl group, a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyl- C_{1-5} alkyl group, a C_{1-5} alkoxy- C_{1-5} alkyl group, a C_{3-8} cycloalkyloxy- C_{1-5} alkyl group or a phenyl group), and

25 Het is any of heterocyclic groups represented by the following formulas form(01) to form(20):



wherein E is CH or N,

R⁴ is a hydrogen atom, a C₁₋₅alkyl group, a C₃₋₈cycloalkyl group, a C₃₋₈cycloalkyl-C₁₋₅alkyl group, a hydroxyl group, a C₁₋₅alkoxy group, a C₃₋₈cycloalkyloxy group, or a group represented by the formula -N(R¹⁰)R¹¹ (wherein each of R¹⁰ and R¹¹, which may be the same or different, is a hydrogen atom, a C₁₋₅alkyl group, a C₃₋₈cycloalkyl group or a C₃₋₈cycloalkyl-C₁₋₅alkyl group), each of R⁵, R⁶, R⁷ and R⁸, which may be the same or different, is a hydrogen atom, a halogen atom, a C₁₋₅alkyl group, a C₃₋₈cycloalkyl group, a C₃₋₈cycloalkyl-C₁₋₅alkyl group, a hydroxyl group, a C₁₋₅alkoxy group, a C₃₋₈cycloalkyloxy group, a group represented by the formula -N(R¹²)R¹³ (wherein each of R¹² and R¹³, which may be the same or different, is a hydrogen atom, a C₁₋₅alkyl group, a C₃₋₈cycloalkyl group or a C₃₋₈cycloalkyl-C₁₋₅alkyl group), a group represented by the formula -CO₂R¹⁴ (wherein R¹⁴ is a hydrogen atom, a C₁₋₅alkyl group, a C₃₋₈cycloalkyl group, a C₃₋₈cycloalkyl-C₁₋₅alkyl group, a C₁₋₅alkoxy-C₁₋₅alkyl group, a C₃₋₈cycloalkyloxy-C₁₋₅alkyl group or a phenyl group), a cyano group, a nitro group, a C₁₋₅alkylthio group, a trifluoromethyl group or a trifluoromethoxy group, R⁹ is a hydrogen atom, a C₁₋₅alkyl group, a C₂₋₅alkenyl group, a C₂₋₅alkynyl group, a C₃₋₈cycloalkyl group or a C₃₋₈cycloalkyl-C₁₋₅alkyl group, and Ar is an aryl or heteroaryl group unsubstituted or substituted with 1 to 3 substituents which may

be the same or different and are selected from halogen atoms, C_{1-5} alkyl groups, C_{1-5} alkoxy groups, C_{1-5} alkylthio groups, trifluoromethyl group, trifluoromethoxy group and groups represented by the formula $-N(R^{15})R^{16}$ (wherein 5 each of R^{15} and R^{16} , which may be the same or different, is a hydrogen atom or a C_{1-5} alkyl group); or a pharmaceutically acceptable salt thereof or its hydrate.

The terms used in the present specification have the following meanings.

10 The term " C_{1-5} alkyl group" means a straight chain or branched chain alkyl group of 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl or the like. The term " C_{2-5} alkenyl group" means a straight chain or 15 branched chain alkenyl group of 2 to 5 carbon atoms, such as vinyl, 1-propenyl, 2-propenyl, 1-methylvinyl or the like. The term " C_{2-5} alkynyl group" means a straight chain or branched chain alkynyl group of 2 to 5 carbon atoms, such as ethynyl, 2-propynyl or the like. The 20 term " C_{3-8} cycloalkyl group" means a cyclic alkyl group of 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like. The term " C_{3-8} cycloalkyl- C_{1-5} alkyl group" means a substituted C_{1-5} alkyl group having the above-mentioned C_{3-8} cycloalkyl 25 group as the substituent, such as cyclopropylmethyl, cyclopropylethyl, cyclopentylethyl or the like.

For B, the term " $N-C_{1-5}$ alkyl" means a group having a C_{1-5} alkyl group as a substituent on the nitrogen

atom. The term "N-C₃₋₈cycloalkyl" means a group having a C₃₋₈cycloalkyl group as a substituent on the nitrogen atom. The term "N-C₁₋₅alkyl-C₃₋₈cycloalkyl" means a group having a C₃₋₈cycloalkyl-C₁₋₅alkyl group as a substituent 5 on the nitrogen atom.

The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. The term "C₁₋₅alkoxy group" means a straight chain or branched chain alkoxy group of 1 to 5 carbon atoms, 10 such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like. The term "C₃₋₈cycloalkyloxy group" means a cyclic alkoxy group of 3 to 8 carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or the like. The term 15 "C₁₋₅alkoxy-C₁₋₅alkyl group" means a substituted C₁₋₅alkyl group having a C₁₋₅alkoxy group as the substituent, such as methoxymethyl, 2-ethoxyethyl or the like. The term "C₃₋₈cycloalkyloxy-C₁₋₅alkyl group" means a substituted C₁₋₅alkyl group having a C₃₋₈cycloalkoxy group as the 20 substituent, such as cyclopropyloxymethyl, 2-cyclopropyloxyethyl or the like. The term "C₁₋₅alkylthio group" means a straight chain or branched chain alkylthio group of 1 to 5 carbon atoms, such as methylthio, ethylthio, propylthio or the like.

25 The term "aryl group" means a phenyl group, a naphthyl group or the like. The term "heteroaryl group" means a heterocyclic group having in its ring 1 to 4 atoms which may be the same or different and are

selected from nitrogen, oxygen and sulfur, such as pyridyl, quinolyl, indolyl, benzofuranyl, benzo-thiadiazolyl, benzofurazanyl, quinoxalinyl or the like. Therefore, the substituted aryl or heteroaryl group

5 includes, for example, 2,4,6-trimethylphenyl group, 2,4,6-tribromophenyl group, 2,4-dibromo-6-chlorophenyl group, 2,4-dichlorophenyl group, 2,4,6-trichlorophenyl group, 2-methyl-4-methoxyphenyl group, 2,4-dibromo-6-fluorophenyl group, 2,4-dibromo-6-methylphenyl group,

10 2,4-dibromo-6-methoxyphenyl group, 2,4-dibromo-6-methylthiophenyl group, 2,6-dibromo-4-isopropylphenyl group, 2,6-dibromo-4-trifluoromethylphenyl group, 2-chloro-4-trifluoromethylphenyl group, 2-chloro-4-trifluoromethoxyphenyl group, 6-dimethylamino-4-

15 methylpyridin-3-yl group, 2-chloro-6-trifluoromethyl-pyridin-3-yl group, 2-chloro-6-trifluoromethoxy-pyridin-3-yl group, 2-chloro-6-methoxy-pyridin-3-yl group, 2-trifluoromethyl-6-methoxy-pyridin-3-yl group, 2-chloro-6-difluoromethyl-pyridin-3-yl group, 2-methyl-6-

20 methoxy-pyridin-3-yl group, 2,6-dimethoxy-pyridin-3-yl group, 5,7-dimethyl-2,1,3-benzothiadiazol-4-yl group, 5,7-dimethylbenzofurazan-4-yl group, 6,8-dimethyl-quinoxalin-5-yl group, 5,7-dichloro-2,1,3-benzo-thiadiazol-4-yl, 5,7-dichlorobenzofurazan-4-yl group

25 and 6,8-dichloroquinoxalin-5-yl group.

The pharmaceutically acceptable salt in the present invention includes, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric

acid, phosphoric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, p-5 toluenesulfonic acid or the like; and salts with a metal ion such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion or the like.

Preferable examples of the compound of the present invention are as follows.

10 That is, preferable are compounds of the formula [I] in which A is a group represented by the formula [II]. More preferable are compounds of the formula [I] in which A is a group represented by the formula [III], Y is a carbamoyl group and n is 0 or 1.

15 In addition, preferable are compounds of the formula [I] in which Het is a heterocyclic group represented by form(01) or form(12). More preferable are compounds of the formula [I] in which Het is a heterocyclic group represented by form(01) or form(12), and Ar is a phenyl

20 group having two or three substituents which may be the same or different and are selected from halogen atoms, C_{1-5} alkyl groups, C_{1-5} alkoxy groups, C_{1-5} alkylthio groups, trifluoromethyl group and trifluoromethoxy group.

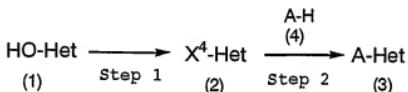
Still more preferable are compounds of the formula [I]

25 in which Het is a heterocyclic group represented by form(01) or form(12), and Ar is a phenyl group having two or three substituents which may be the same or different and are selected from chlorine atom,

trifluoromethyl group and trifluoromethoxy group.

The compound of the formula [I] can be produced, for example, by any of the processes shown in the following reaction schemes 1 to 7 (in the following 5 reaction schemes, A, Het, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ are as defined above, R¹⁷ is a C₁₋₅alkyl group or a phenyl group, and X⁴ is a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group, a benzene-sulfonyloxy group, a toluenesulfonyloxy group or a 10 trifluoromethanesulfonyloxy group).

Reaction Scheme 1.



Step 1:

Compound (2) can be obtained by halogenation 15 or sulfonylation of the hydroxyl group of Compound (1). Here, the halogenation refers to reaction with a halogenating reagent such as phosphorus oxychloride, phosphorus pentachloride, sulfonyl chloride, thionyl chloride, thionyl bromide, oxaly chloride or the like 20 in the presence or absence of, for example, N,N-dimethylaniline or N,N-diethylaniline without a solvent or in an inert solvent such as a hydrocarbon (e.g., benzene and toluene) or a halogen-containing solvent (e.g., chloroform and dichloromethane). The sulfonylation refers to reaction with a sulfonylating reagent 25

such as methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic acid anhydride, N-phenylbis(trifluoromethanesulfonimide) or the like in the presence or absence of a base in an inert solvent

5 such as an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene), an amide (e.g., N,N-dimethylformamide and N-methylpyrrolidone), acetonitrile, dimethyl sulfoxide, pyridine, or a

10 mixture of solvents selected from these inert solvents. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the like; and inorganic bases such as sodium hydride, potassium

15 hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like.

Step 2:

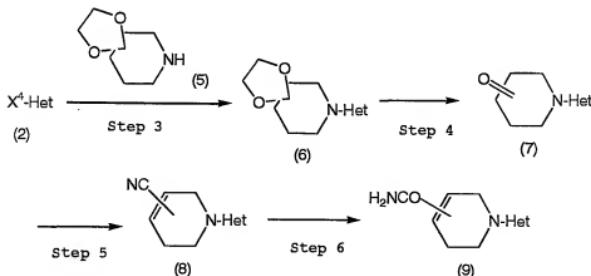
Compound (3), the compound of the present invention, can be obtained by reacting Compound (2)

20 with Compound (4) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide,

sodium ethoxide, potassium tert-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Compound (9) of the present invention can be synthesized according also to the following reaction scheme 2.

Reaction Scheme 2



Step 3:

Compound (6) can be obtained by reacting Compound (2) with Compound (5) in an inert solvent in

the presence or absence of a base. Here, the base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, 5 sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal amides such as sodium amide, lithium diisopropyl-10 amide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydro-15 furan, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methyl-pyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents 20 selected from these inert solvents.

Step 4:

Compound (6) can be converted to Compound (7) by removing the acetal protective group of Compound (6) by conventional hydrolysis under acidic conditions (see 25 Theodora W. Greene and Peter G. W. Wuts "Protective Groups in Organic Synthesis").

Step 5:

Compound (7) can be converted to Compound (8) by reacting Compound (7) in the presence of a cyanating agent such as sodium cyanide, potassium cyanide, 5 trimethylsilyl cyanide or the like in an inert solvent such as an alcohol (e.g., methanol, ethanol, isopropyl alcohol and ethylene glycol), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), acetonitrile, acetic acid, water, or 10 a mixture of solvents selected from these inert solvents; and then reacting the cyanation product with, for example, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoroacetic anhydride in the presence or absence of 15 an organic base such as pyridine, triethylamine or diisopropylethylamine in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), 20 a hydrocarbon (e.g., benzene and toluene) or the like.

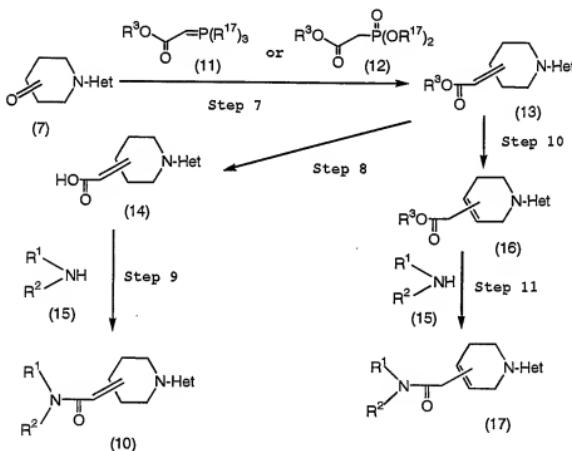
Step 6:

Compound (8) can be converted to Compound (9) of the present invention by reacting the cyano group of Compound (8) by using, for example, sulfuric acid, 25 hydrogen chloride and formic acid singly or in combination of two or more thereof, in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane

and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene), water or a mixture of solvents selected from these inert solvents.

5 In addition, Compound (10) and Compound (17) of the present invention can be obtained according also to the following reaction scheme 3.

Reaction Scheme 3



10 Step 7:

Compound (7) can be converted to Compound (13) by reacting Compound (7) with either Compound (11) or Compound (12) in an inert solvent in the presence or absence of a base. Here, the base includes, for 15 example, sodium hydride, potassium hydride, sodium

methoxide, potassium tert-butoxide, n-butyllithium, lithium bis(trimethylsilyl)amide, sodium amide and potassium carbonate. If necessary, 18-crown-6 ether, 15-crown-5 ether, tetramethylethylenediamine, 5 hexamethylphosphoramide and the like can be used as an additive. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as 10 ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; water; and mixtures of solvents selected from these inert solvents.

15 Step 8:

When R³ of Compound (13) is a group other than a hydrogen atom, Compound (13) can be converted to Compound (14) of the present invention by conventional hydrolysis of the ester portion under acidic or basic 20 conditions (see Theodora W. Greene and Peter G. W. Wuts "Protective Groups in Organic Synthesis").

Step 9:

Compound (10) of the present invention can be obtained by amidation of Compound (14). Here, the 25 amidation refers to general amidation of the carboxyl group, and refers to any of the following reactions:

the reaction of Compound (15) with a mixed acid anhydride obtained by the reaction of Compound (14) with a haloformic acid ester (e.g., ethyl chloroformate and isobutyl chloroformate) or an acid halide (e.g., 5 benzoyl chloride and pivaloyl chloride) in the presence of a base such as N-methylmorpholine, triethylamine or the like; the reaction of Compound (14) with Compound (15) in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethyl-10 aminopropyl)-3-ethylcarbodiimide (EDC), carbonyl-diimidazole (CDI), diphenylphosphorylazide (DPPA), diethyl cyanophosphate or the like and optionally an additive such as 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide, 4-dimethylaminopyridine or the 15 like; and the reaction of Compound (15) with an acid halide obtained by the reaction of Compound (14) with a halogenating reagent such as thionyl chloride, oxalyl chloride, carbon tetrabromide-triphenylphosphine or the like.

20 Step 10:

Compound (13) can be converted to Compound (16) by reacting Compound (13) in the presence of an acid or a base in an inert solvent. Here, the acid includes, for example, inorganic acids such as hydrogen 25 chloride, hydrobromic acid, sulfuric acid and the like; and organic acids such as acetic acid, trifluoroacetic acid, p-toluenesulfonic acid and the like. The base

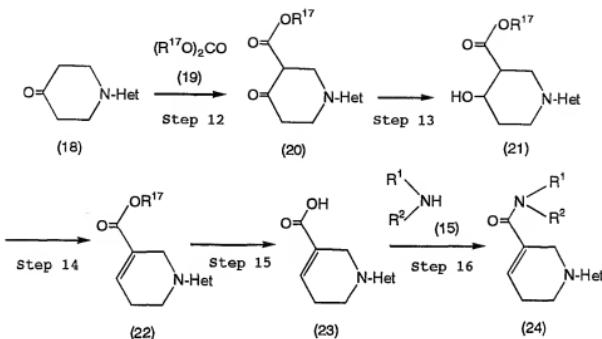
includes inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and 5 the like; hydrocarbons such as benzene, toluene and the like; alcohols such as ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methyl-pyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; water; acetone; and mixtures of solvents 10 selected from these inert solvents. When R³ is a group other than a hydrogen atom, employment of a solvent for reaction composed of water alone or a mixture of water and one or more other solvents makes it possible to carry out the conversion of R³ to a hydrogen atom and 15 the conversion of Compound (13) to Compound (16) simultaneously.

Step 11:

When R³ is a group other than a hydrogen atom, R³ is converted to a hydrogen atom by the same procedure 20 as in Step 8, after which Compound (17) of the present invention can be obtained by the same reaction as in Step 9.

Compounds (22), (23) and (24) can be synthesized according also to the following reaction 25 scheme 4.

Reaction Scheme 4



Step 12:

Compound (20) can be obtained by reacting Compound (18) with Compound (19) in an inert solvent in the presence of a base. Here, the inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; and mixtures of solvents selected from these inert solvents. The base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine and the like; inorganic bases such as sodium hydride, potassium hydride, sodium carbonate and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkyl metals such as n-butyllithium, tert-butyllithium, phenyllithium and

the like; and metal amides such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium amide and the like.

Step 13:

5 Compound (20) can be converted to Compound (21) by reduction of the ketone portion represented by hydride reduction using sodium boron hydride, and hydrogenation (see Ahmed F. Abdel-Magid "Reductions in Organic Synthesis").

10 Step 14:

Compound (21) can be converted to Compound (22) by reacting Compound (21) with, for example, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride or 15 trifluoroacetic anhydride in the presence or absence of an organic base such as pyridine, 4-dimethylamino-pyridine, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like in an inert solvent such as a halogen-containing solvent (e.g., 20 dichloromethane and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene) or the like, or by reacting Compound (21) with, for example, sulfuric acid, trifluoroacetic acid 25 or formic acid in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane and chloro-

form), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene) or the like.

Step 15:

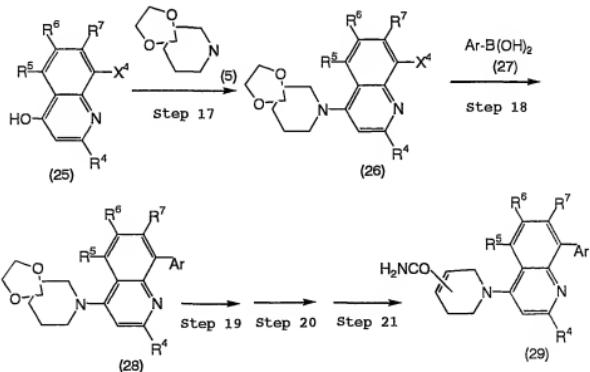
5 Compound (22) can be converted to Compound (23) of the present invention by converting the ester portion of Compound (22) to a carboxyl group by the same procedure as in Step 8.

Step 16:

10 Compound (23) can be converted to Compound (24) of the present invention by reacting Compound (23) with Compound (15) by the same procedure as in Step 9.

15 Compound (29) of the present invention can be synthesized according also to the following reaction scheme 5.

Reaction Scheme 5



Step 17:

Compound (26) can be obtained by halogenating or sulfonylating the hydroxyl group of Compound (25) by the same procedure as in Step 1, and then reacting the 5 halogenation or sulfonylation product with Compound (5) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the 10 like; and inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; and mixtures of solvents selected from these inert 15 20 solvents.

Step 18:

Compound (26) can be converted to Compound (28) by reacting Compound (26) with an aryl-boric acid derivative (27) in an inert solvent in the presence of 25 a base, a zero-valence palladium complex (e.g., tetrakis(triphenylphosphine)palladium and tetrakis-(tributylphosphine)palladium) or a divalent palladium

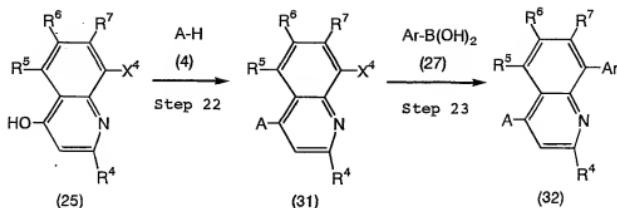
complex (e.g., palladium acetate and palladium chloride) and optionally a phosphine (e.g., triphenylphosphine and tributylphosphine). Here, the base includes, for example, inorganic bases such as sodium 5 carbonate, sodium hydrogencarbonate, potassium carbonate, barium hydroxide, sodium hydroxide and the like; and organic bases such as triethylamine, diisopropylethylamine, pyridine, 4-dimethylamino-pyridine and the like. The inert solvent includes, for 10 example, halogen-containing solvents such as dichloromethane, chloroform and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as 15 methanol, ethanol and the like; water; and mixtures of solvents selected from these inert solvents.

Step 19, Step 20 and Step 21:

Compound (29) of the present invention can be obtained by carrying out Step 19, Step 20 and Step 21 20 in the same manner as for Step 4, Step 5 and Step 6, respectively.

Compound (32) of the present invention can be synthesized according also to the following reaction scheme 6.

Reaction Scheme 6



Step 22:

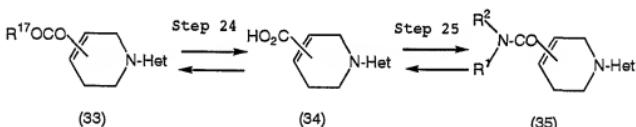
Compound (31) can be obtained by halogenating or sulfonylating the hydroxyl group of Compound (25) by the same procedure as in Step 1, and then reacting the halogenation or sulfonylation product with Compound (4) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the like; and inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; and mixtures of solvents selected from these inert solvents.

Step 23:

Compound (32) of the present invention can be obtained by the same procedure as in Step 18.

Compounds (33), (34) and (35) of the present invention can be synthesized according also to the following reaction scheme 7.

Reaction Scheme 7



Step 24:

10 Compounds (33) and (34) of the present
invention can be converted to each other by conven-
tional protection and deprotection of the ester portion
and the carboxylic acid portion (see Theodora W. Greene
and Peter G. W. Wuts "Protective Groups in Organic
15 Synthesis").

Step 25:

Compound (34) of the present invention can be converted to Compound (35) of the present invention by conventional amidation in the same manner as in Step 9.

20 Compound (35) can be converted to Compound (34) by
converting the amide portion of Compound (35) to a
carboxylic acid by conventional hydrolysis (see
Theodora W. Greene and Peter G. W. Wuts "Protective

Groups in Organic Synthesis").

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved.

5 For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, 10 disintegrators, pH-adjusting agents, solvents, etc.

The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or parenterally. The dose can be properly 15 increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is concretely explained 20 with reference to the following examples and test example, but is not limited thereto.

Example 1

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-25 quinoline (compound 1-01)

After 60% sodium hydride (an oil dispersion)

(79 mg) was washed with hexane and then suspended in N,N-dimethylformamide (3 mL), the suspension was cooled with ice. To the cooled suspension was added 8-(2,4-dichlorophenyl)-2-methyl-4-hydroxyquinoline (500 mg) 5 all at once, and the resulting mixture was stirred under ice-cooling for 10 minutes and then at room temperature for another 30 minutes. To the solution thus obtained was added N-phenylbis(trifluoromethane-sulfonimide) (703 mg) all at once, and the resulting 10 mixture was stirred at room temperature for 30 minutes.

To the resultant reaction mixture were added sodium hydrogencarbonate (413 mg) and 4-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (533 mg), and the resulting mixture was vigorously stirred at 120°C 15 for 1 hour.

The reaction mixture thus obtained was cooled to room temperature and then separated with chloroform and water. The aqueous layer was extracted with chloroform and the combined organic layer was dried 20 over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 25 10 : 1), and the crystals thus obtained were washed with methanol and then tetrahydrofuran to obtain the title compound (156 mg).

m.p. 263.5 - 265.5°C.

Table 1, Table 2, Table 7, Table 17 and Table 18 list the compound obtained in Example 1 and compounds obtained by the same procedure as in Example 1.

5 Example 2

Synthesis of 8-(2,4-dichlorophenyl)-4-(5-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-quinoline (compound 1-15)

(1) In phosphorus oxychloride (5 mL), 8-10 (2,4-dichlorophenyl)-2-methyl-4-hydroxyquinoline (2.0 g) was heated under reflux for 1 hour. The reaction mixture was cooled to room temperature and carefully poured into ice water, and the resulting mixture was separated with a saturated aqueous sodium hydrogen-15 carbonate solution and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure to obtain a solid (2.1 g).

20 (2) A mixture of the solid (200 mg) obtained in (1), 5-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (121 mg), diisopropylethylamine (240 mg) and ethanol (1 mL)-water (0.075 mL) was allowed to react in a sealed tube at 80°C for 10 days. The reaction mixture 25 was cooled to room temperature, poured into a saturated aqueous sodium hydrogencarbonate solution, and then extracted three times with chloroform. The combined

organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column 5 chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1) and then crystallized from ethyl acetate to obtain the title compound (159 mg).

m.p. 230.0 - 232.0°C.

10 Table 1, Table 2, Tables 3 to 11, Table 13, Table 16, Table 19 and Table 20 list the compound obtained in Example 2 and compounds obtained by the same procedure as in Example 2.

Example 3

15 Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-quinoline (compound 1-01)

(1) In N,N-dimethylformamide (50 mL), 4-chloro-8-(2,4-dichlorophenyl)-2-methylquinoline (3.3 g) 20 obtained by the same procedure as in Example 2, (1) and 4-piperidone ethylene ketal (7.5 g) were stirred at 120°C for 2 hours and then at 150°C for 2 hours, and the resulting mixture was heated under reflux for 3.5 hours. The solvent was distilled off under reduced 25 pressure, after which water and a saturated aqueous sodium hydrogencarbonate solution were added to the residue and the solid precipitated was collected by

filtration. The obtained solid was purified by a silica gel column chromatography (silica gel: Wako Gel C200); eluent: chloroform-methanol = 10 : 1) to obtain 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-5-yl)-2-methylquinoline (3.2 g).

m.p. 179.5 - 181.5°C.

(2) In a mixture of 1 M hydrochloric acid (30 mL) and tetrahydrofuran (15 mL), 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (3.2 g) was stirred at room temperature for 2 hours and then at 70°C for 5.5 hours. The tetrahydrofuran was distilled off under reduced pressure, and the residue was made basic with a 41% aqueous sodium hydroxide solution under ice-cooling and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in ethanol (12.5 mL)-chloroform (6 mL), and potassium cyanide (5.4 g) was added thereto. To the mixture thus obtained was added acetic acid (4.4 mL) under ice-cooling over a period of 10 minutes, and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution and the organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was

filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in pyridine (15 mL), and phosphorus oxychloride (7.5 mL)

5 was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 24 hours and then carefully poured into ice water. The reaction mixture thus treated was extracted three times with a mixed solvent of chloroform and methanol, and the 10 combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), 15 eluent: hexane-ethyl acetate = 5 : 1) and then crystallized from diisopropyl ether to obtain 8-(2,4-dichlorophenyl)-2-methyl-4-(4-cyano-1,2,3,6-tetrahydro-pyridin-1-yl)quinoline (1.0 g).

m.p. 177.5 - 179.5°C.

20 (3) In 96% formic acid (5 mL) was dissolved 8-(2,4-dichlorophenyl)-2-methyl-4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)quinoline (1.0 g), and hydrogen chloride gas was bubbled into the solution under ice-cooling to saturate the solution therewith. The 25 reaction mixture was stirred at room temperature for 4 hours and then distilled under reduced pressure to remove the solvent. The residue was separated with chloroform and a saturated aqueous sodium hydrogen-

carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a 5 silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1) and then recrystallized from tetrahydrofuran to obtain the title compound (174 mg).

m.p. 263.5 - 265.5°C.

10 Table 1 and Table 14 list the compound obtained in Example 3 and a compound obtained by the same procedure as in Example 3.

Example 4

Synthesis of 4-(4-carbamoyl-1,2,3,6-

15 tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (compound 12-01)

(1) After 60% sodium hydride (an oil dispersion) (0.97 g) was washed with hexane and then suspended in N,N-dimethylformamide (10 mL), a solution 20 of 1-(2,4-dichlorophenyl)-4-hydroxy-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (6.50 g) in N,N-dimethyl-formamide (90 mL) was added dropwise thereto. The resulting mixture was stirred at 40°C for 30 minutes, after which N-phenylbis(trifluoromethanesulfonimide) 25 (8.65 g) was added thereto all at once, followed by stirring at room temperature for 30 minutes. To the solution thus obtained was added 4-piperidone ethylene

ketal (16.4 g), and the reaction was carried out at 90°C for 2 hours, at 100°C for 1.5 hours, and then at 120°C for 2.5 hours. After the reaction mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution was poured thereinto, followed by extraction with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 3 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (5.23 g).

(2) After 1-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (5.21 g) was stirred in a mixture of 4 M hydrochloric acid (60 mL) and tetrahydrofuran (60 mL) at room temperature for 2.5 hours, 6 M hydrochloric acid (30 mL) was added thereto and the resulting mixture was stirred overnight. After completion of the reaction, the reaction mixture was poured into a saturated aqueous sodium hydrogen-carbonate solution and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The crystals thus

obtained were washed with ethyl acetate to obtain 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (3.83 g).

(3) In ethanol (10 mL)-chloroform (4 mL) was dissolved 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.55 g), and potassium cyanide (0.91 g) was added thereto. To the resulting mixture was added acetic acid (0.75 mL) under ice-cooling over a period of 15 minutes, followed by stirring at room temperature for 2 hours. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution and the organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in pyridine (6.4 mL), and phosphorus oxychloride (1.3 mL) was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 1 hour and then at 60°C for 1 hour. The reaction mixture was carefully poured into ice water and extracted three times with ethyl acetate, and the combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-

ethyl acetate = 4 : 1) to obtain 4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.33 g).

(4) In methylene chloride (2.0 mL) was dissolved 4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.19 g), followed by adding thereto concentrated sulfuric acid (0.5 mL) under ice-cooling, and the resulting mixture was slowly heated to room temperature and then stirred overnight. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and the desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel C200, eluent: chloroform-methanol = 30 : 1) and the crystals precipitated were washed with ethyl acetate to obtain the title compound (0.10 g).

m.p. 265.0 - 267.0°C.

Table 11 and Table 12 list the compound obtained in Example 4 and compounds obtained by the same procedure as in Example 4.

Example 5

Synthesis of 4-(5-carbamoyl-1,2,3,6-

tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (compound 12-09)

(1) After 60% sodium hydride (an oil dispersion) (79 mg) and a small amount of 35% potassium 5 hydride (an oil dispersion) were washed twice with hexane, tetrahydrofuran (2.0 mL) and diethyl carbonate (0.21 g) were added thereto and the resulting mixture was heated at 80°C. Then, a solution of 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-10 trimethyl-1H-pyrrolo[2,3-b]pyridine (0.29 g) synthesized by the same procedure as in Example 4 in tetrahydrofuran (2.0 mL) was added dropwise thereto over a period of 10 minutes, and the resultant mixture was heated under reflux for 1.5 hours. After the 15 reaction mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The 20 desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 4 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(3-ethoxy-25 carbonyl-4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.14 g).

(2) In ethanol (3.0 mL) was dissolved 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-

oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.13 g), and the solution was cooled to -15°C. Then, sodium boro hydride (26 mg) was added thereto and the resulting mixture was stirred overnight 5 while being slowly heated to 0°C. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent 10 was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 50 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-hydroxy- 15 1-piperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (35 mg).

(3) In methylene chloride (1.5 mL) were dissolved 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-hydroxypiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (53 mg), triethylamine (34 mg) and a small amount of 4-dimethylaminopyridine. Methanesulfonyl chloride (25 mg) was added thereto and the resulting mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium hydrogen carbonate solution was 20 poured into the reaction mixture, which was then extracted three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate 25

was concentrated under reduced pressure. The residue was dissolved in benzene (1.0 mL), followed by adding thereto 1,8-diazabicyclo[5.4.0]-7-undecene (17 mg), and the resulting mixture was heated under reflux for 1
5 hour. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and
10 the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 5 : 1) to obtain 4-(5-ethoxy-
15 carbonyl-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-
dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-
b]pyridine (27 mg).

(4) In ethanol (1.0 mL) was dissolved 4-(5-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-
20 dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-
b]pyridine (27 mg), followed by adding thereto a 1 M aqueous sodium hydroxide solution (1.0 mL), and the resulting mixture was stirred at room temperature for 8.5 hours. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which
25 was then extracted three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was suspended in a mixed solvent of N,N-dimethylformamide (0.8 mL) and chloroform (0.2 ml), and 1-hydroxybenzotriazole monohydrate (18 mg) and 1-(3-dimethylaminopropyl)-3-5 ethylcarbodiimide hydrochloride (23 mg) were added thereto. After the resulting mixture was stirred at room temperature for 40 minutes, a few drops of 28% aqueous ammonia solution was added thereto, and the mixture thus obtained was stirred at room temperature 10 for 1.5 hours. A saturated aqueous sodium hydrogen-carbonate solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent 15 was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 1 : 2) and crystallized from a mixed solvent of diisopropyl ether 20 and ethyl acetate to obtain the title compound (6.0 mg).

Table 12 lists the compound obtained in Example 5.

Example 6

25 Synthesis of 5-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-(N-ethyl-2,4-dichloro-anilino)-4-methylthiazole (compound 15-01)

(1) After 2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole hydrochloride (6.0 g) and calcium carbonate (4.6 g) were suspended in a mixed solvent of chloroform (90 mL) and methanol (36 mL), benzyl-5 trimethylammonium tribromide (7.2 g) was added thereto in small portions. The solids in the reaction mixture were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel 10 (C200), eluent: hexane-ethyl acetate = 9 : 1) to obtain 5-bromo-2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole (4.5 g).

(2) A mixture of 5-bromo-2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole (0.20 g), 5-15 carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (178 mg), sodium hydrogencarbonate (94 mg) and ethanol (1.5 mL) was allowed to react in a sealed tube at 120°C for 3 days. The reaction mixture was separated with water and chloroform and the aqueous layer was extracted with 20 chloroform, after which the combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica 25 gel: Wako Gel (C200), eluent: chloroform-methanol = 20 : 1) and then crystallized from diisopropyl ether to obtain the title compound (34 mg).

m.p. 148.0 - 150.0°C.

Table 15 lists the compound obtained in Example 6.

Example 7

Synthesis of 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}-acetamide (compound 1-22) and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}-acetamide (compound 1-05)

(1) In a mixture of 1 M hydrochloric acid (26 mL) and tetrahydrofuran (13 mL), 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (2.6 g) obtained by the same procedure as in Example 3, (1) was stirred at room temperature for 2 hours and then at 70°C for 5.5 hours. The tetrahydrofuran was distilled off under reduced pressure, and the residue was made basic with a 41% aqueous sodium hydroxide solution under ice-cooling and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in tetrahydrofuran (10 mL) and the resulting solution was added dropwise to a solution of Horner-Emmons reagent that had previously been prepared from ethyl diethyl-phosphonoacetate (2.05 g) and 60% sodium hydride (an oil dispersion) (293 mg) in tetrahydrofuran (10 mL),

under ice-cooling over a period of 20 minutes. The ice bath was removed, and the reaction mixture was stirred at room temperature for 30 minutes, quenched with a saturated aqueous ammonium chloride solution, and then 5 extracted twice with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The resultant residue was purified by a silica gel 10 column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 9 : 1) and then crystallized from diisopropyl ether to obtain 8-(2,4-dichlorophenyl)-2-methyl-4-(4-ethoxycarbonyl-methylidene)piperidin-1-yl)quinoline (2.4 g).

15 (2) In a mixed solvent of 85% potassium hydroxide (1.3 g) and water (1.4 mL)-ethanol (8 mL), 8-(2,4-dichlorophenyl)-2-methyl-4-(4-ethoxycarbonyl-methylidene)piperidin-1-yl)quinoline (2.3 g) was stirred at 80°C for 1 hour. The reaction mixture was 20 neutralized with 3 M hydrochloric acid under ice-cooling and stirred under ice-cooling for 2 hours and then at room temperature for 30 minutes. The solid precipitated was collected by filtration to obtain a mixture (1.5 g) of 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}acetic acid and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}acetic acid.

25 (3) A mixture (400 mg) of 2-{1-[8-(2,4-

dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}acetic acid and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}acetic acid, 1-hydroxybenzotriazole monohydrate (215 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215 mg) were stirred in N,N-dimethyl-formamide (2 mL) at room temperature for 20 minutes. Then, a 28% aqueous ammonia solution (0.075 mL) was added thereto and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was separated with chloroform and water, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was separated and purified twice by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-ethanol = 50 : 1), after which the purified products were crystallized from diethyl ether and diisopropyl ether, respectively, to obtain the title compound 1-22 (109 mg) and the title compound 1-05 (43 mg), respectively.

Compound 1-22: m.p. 225.0 - 227.0°C.

Compound 1-05: m.p. 160.0 - 162.0°C.

Table 1 and Table 16 list the compounds obtained in Example 7 and compounds obtained by the same procedure as in Example 7.

Example 8

Synthesis of 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline

(1) After having been washed with hexane,
5 60% sodium hydride (an oil dispersion) (1.68 g) was suspended in N,N-dimethylformamide (20 mL). To the resulting suspension was added a suspension of 8-bromo-4-hydroxy-2-methylquinoline (10.0 g) in N,N-dimethylformamide (35 mL) at room temperature over a period of
10 10 minutes, followed by stirring at room temperature for 30 minutes. To the resultant solution was added N-phenylbis(trifluoromethanesulfonimide) (15.0 g) all at once, followed by stirring at room temperature for 1 hour.

15 To the resultant reaction mixture was added 4-piperidone ethylene ketal (11.0 g), and the resulting mixture was stirred at room temperature for 24 hours and heated under reflux at 60°C for 4 hours and then for 2.5 hours. After 4-piperidone ethylene ketal (5.5 g)
20 was added thereto, the mixture thus obtained was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature, poured into water (200 ml) and then stirred for 24 hours. The solid precipitated was collected by filtration and purified by a silica
25 gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 5 : 1 to 3 : 1) to obtain 8-bromo-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (10.3 g), m.p. 156.0 - 158.0°C.

(2) Under a nitrogen atmosphere, 8-bromo-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (10.2 g), 2,4-dichlorophenylboric acid (6.0 g) and sodium carbonate (8.93 g) were suspended in a mixed solvent of deaerated water (24 mL), toluene (12 mL) and ethanol (12 mL), followed by adding thereto tetrakis(triphenylphosphine)palladium (1.6 g), and the resulting mixture was heated under reflux for 16 hours. The reaction mixture was cooled to room temperature and separated with ethyl acetate and a saturated aqueous ammonium chloride solution. After the aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure and the resultant residue was crystallized from diisopropyl ether. The crystals were collected by filtration and washed with a small amount of diisopropyl ether to obtain the title compound (10.5 g).

20 m.p. 179.5 - 181.5°C.

Example 9

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-01)

25 (1) After having been washed with hexane, 60% sodium hydride (an oil dispersion) (1.0 g) was suspended in N-methylpyrrolidone (40 mL). To the

suspension was added 8-bromo-4-hydroxy-2-methyl-
quinoline (5.0 g) all at once at room temperature,
followed by stirring at room temperature for 1 hour.
To the resulting solution was added N-phenylbis-
5 (trifluoromethanesulfonimide) (15.0 g) all at once,
followed by stirring at room temperature for 1 hour.

To the resultant reaction mixture were added
sodium hydrogencarbonate (5.3 g) and 4-carbamoyl-
1,2,3,6-tetrahydropyridine hydrochloride (6.8 g), and
10 the resulting mixture was stirred at 130°C for 30
minutes. After this reaction mixture was cooled to
room temperature, water (100 mL) was added thereto,
followed by stirring at room temperature for 2 hours.
The solid precipitated was collected by filtration and
15 then washed with water to obtain 8-bromo-4-(4-
carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-
quinoline (4.8 g).

m.p. 225.0 - 227.0°C.

(2) Under a nitrogen atmosphere, 8-bromo-2-
20 methyl-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-
yl)quinoline (4.7 g), 2,4-dichlorophenylboric acid (2.9
g) and sodium carbonate (4.5 g) were suspended in a
mixed solvent of deaerated water (14 mL), toluene (7
mL) and ethanol (7 mL), followed by adding thereto
25 tetrakis(triphenylphosphine)palladium (0.81 g), and the
resulting mixture was heated under reflux for 5 hours.
The reaction mixture was cooled to room temperature and
stirred at room temperature for 3 hours. The solid

precipitated was collected by filtration and washed with a water-ethanol (2 : 1) mixed solvent (30 mL) and then ethanol (30 mL) to obtain the title compound (4.7 g).

5 Table 1 lists the compound obtained in
Example 9.

Example 10

10 Synthesis of 8-(2,4-dichlorophenyl)-4-(4-isopropylloxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-14)

(1) After having been washed with hexane, 60% sodium hydride (an oil dispersion) (1.0 g) was suspended in N-methylpyrrolidone (30 mL). To the suspension was added 8-bromo-4-hydroxy-2-methyl-15 quinoline (5.0 g) all at once at room temperature, followed by stirring at room temperature for 1 hour. To the resulting solution was added N-phenylbis-(trifluoromethanesulfonimide) (9.0 g) all at once, followed by stirring at room temperature for 1 hour.

20 To the resultant reaction mixture was added 4-isopropylloxycarbonyl-1,2,3,6-tetrahydropyridine (8.5 g), and the resulting mixture was stirred overnight at room temperature. This reaction mixture was poured into a mixture of water and ethyl acetate to be 25 separated. After the aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent

was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 9 : 1), and the 5 solid thus obtained was washed with a mixture of diisopropyl ether and hexane to obtain 8-bromo-4-(4-isopropylloxy carbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (6.0 g).

m.p. 130.0 - 131.0°C.

10 (2) Under a nitrogen atmosphere, 8-bromo-4-(4-isopropylloxy carbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (5.9 g), 2,4-dichlorophenylboric acid (3.2 g) and sodium carbonate (4.8 g) were suspended in a mixed solvent of deaerated water (15 mL), toluene (7.5 mL) and ethanol (7.5 mL), followed by adding thereto tetrakis(triphenylphosphine)palladium (0.88 g), and the resulting mixture was heated under reflux for 5 hours. The reaction mixture was cooled to room temperature to be separated. After the aqueous 15 phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure and the resultant residue was crystallized from diisopropyl acid. The crystals were collected by filtration and washed with a small amount of diisopropyl ether to obtain the title compound (5.3 g).

m.p. 131.0 - 133.0°C.

Table 1 lists the compound obtained in
Example 10.

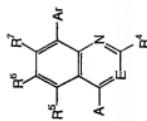
Example 11

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-
5 carboxy-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-
quinoline (compound 1-11)

In concentrated hydrochloric acid (10 mL) was
suspended 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-
1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (0.10
10 g), and the suspension was heated under reflux for 1
hour. After the reaction mixture was concentrated
under reduced pressure, 28% aqueous ammonia (2 mL) was
added thereto, followed by concentration under reduced
pressure. The residue was purified by a silica gel
15 column chromatography (silica gel: Wako Gel (C200),
eluent: chloroform-methanol = 20 : 1 to 10 : 1), and
the solid precipitated was washed with ethyl acetate to
obtain the title compound (74 mg).

m.p. 218.0 - 220.0°C.

20 Table 1 lists the compound obtained in
Example 11.

Table 1¹

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	R ⁷	Ar	Melting point (°C) (solvent for crystallization)
1-01	1, 3, 9	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		263.5-265.5 (MeOH)
1-02	2	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		220.5-222.5 (AcOEt)
1-03	2	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		242.0-244.0 (MeOH)
1-04	2	H ₂ NCO—C ₆ H ₄ —N—	N	CH ₃	H	H	H		220.0-222.0 (Et ₂ O)
1-05	7	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		160.0-162.0 (TPE)
1-06	1	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		235.0-236.0 (MeOH)
1-07	1	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		215.0-216.0 (MeOH)
1-08	1	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	H	H		228.0-230.0 (MeOH)
1-09	1	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	C1	H		256.0-258.0 (MeOH)
1-10	1	H ₂ NCO—C ₆ H ₄ —N—	CH	CH ₃	H	CH ₃	H		252.0-254.0 (MeOH)

Table 1^{a1} (Cont'd)

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	R ⁷	Ar	Melting point (°C) (solvent for crystallization)
1-11	11	HOCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		218.0-220.0 (AcOEt)
1-12	1	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	F	H		273.0-275.0 (MeOH)
1-13	1	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	OCCF ₃	H		235.0-236.0 (MeOH)
1-14	10	PhOCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		131.0-133.0 (IPM/hexane)
1-15	2	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		230.0-232.0 (AcOEt)
1-16	2	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		144.5-146.5 (AcOEt)
1-17	2	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		140.5-142.5 (Et ₂ O)
1-18	2	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	H	H		185.0-187.0 (Et ₂ OH)
1-19	2	H ₂ NCO— C ₆ H ₄ —N—	N	CH ₃	H	H	H		Amorphous ^{a2}
1-20	1	H ₂ NCO— C ₆ H ₄ —N—	CH	CH ₃	H	F	H		237.0-238.0 (MeOH)

Table 1¹ (Cont'd)

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	R ⁷	Ar	Melting point (°C) (solvent for crystallization)
1-21	1	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	H	OCF ₃	H	Cl- C ₆ H ₄ -Cl	170.0-173.0 (EtOH) ^{1,3}
1-22	7	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	H	H	H	Cl- C ₆ H ₄ -Cl	225.0-227.0 (Et ₂ O)
1-23	1	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	H	N(CH ₃) ₂	H	Cl- C ₆ H ₄ -Cl	202.0-204.0 (EtOH)
1-24	1	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	H	N(CH ₃) ₂	H	Cl- C ₆ H ₄ -Cl	187.0-189.0 (IPA/AcOEt) ^{1,3}
1-25	1	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	F	H	H	Cl- C ₆ H ₄ -Cl	244.0-246.0 (EtOH)
1-26	1	H ₂ NCO- C ₆ H ₄ -N-	CH	CH ₃	F	H	H	Cl- C ₆ H ₄ -Cl	214.0-216.0 (EtOH)
1-27	1	H ₂ NCO- C ₆ H ₄ -N-	CH	H	H	H	H	Cl- C ₆ H ₄ -Cl	>235 (decomposed) (EtOH)
1-28	1	H ₂ NCO- C ₆ H ₄ -N-	CH	H	H	H	H	Cl- C ₆ H ₄ -Cl	220.5-222.5 (EtOH)

Table 1* (Cont'd)

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	R ⁷	Ar	Melting point (°C) (solvent for crystallization)
1-29	1	H ₂ NCO-	CH	NH ₂	H	H	H		>230(decomposed)(MeOH)
1-30	1	H ₂ NCO-	CH	NH ₂	H	H	H		155.0-158.5(TPA/Et ₂ O)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization; MeOH = methanol, EtOH = ethanol, ACOEt = ethyl acetate, Et₂O = diethyl ether

*2: ¹H NMR (200MHz, CDCl₃); δ 2.41(3H, s), 2.48-2.66(2H, m), 3.72-3.95(2H, m), 4.34-4.46(2H, m), 6.76-6.87(1H, m), 7.05(1H, br, s), 7.42(1H, d, J=8.4Hz), 7.41-7.63(3H, m), 7.68(1H, dd, J=1.3, 7.3Hz), 7.72(1H, d, J=1.8Hz), 8.04(1H, dd, J=1.3, 8.4Hz).

MS (ES, Pos); 435(M+Na)⁺, 437(M+Na+2)⁺, 439(M+Na+4)⁺

*3: HCl salt

Table 2^{*1}

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	Ar	Melting point (°C) (solvent for crystallization)
2-01	2	H ₂ NCO- cyclohexyl-	N	CH ₃	H	H		221.0-223.0(AcOEt)
2-02	1	H ₂ NCO- cyclohexyl-	CH	CH ₃	H	H		277.0-279.0(AcOEt)
2-03	2	H ₂ NCO- cyclohexyl-	N	CH ₃	H	H		100.0-102.0(IPEx)

*1: Com. No. = compound number, Ex. No. = example number,
solvent for crystallization; AcOEt = ethyl acetate, IPEx = diisopropyl ether

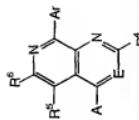
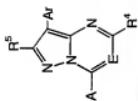


Table 3¹



Com. No.	Ex.No.	A	E	R ⁴	R ⁵	Ar	Melting point (°C) (solvent for crystallization)
3-01	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —CH ₃	245.0—247.0 (AcOEt/IPE)
3-02	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	N	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —Cl	245.0—247.0 (AcOEt/IPE)
3-03	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —Cl	252.0—254.0 (AcOEt)
3-04	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	N	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —Cl	255.0—257.0 (AcOEt)
3-05	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —CH ₃	187.0—189.0 (AcOEt/IPE)
3-06	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	N	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —CH ₃	145.0—147.0 (EtOH/AcOEt) ²
3-07	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —Cl	150.0—152.0 (AcOEt)
3-08	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	N	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —Cl	209.0—211.0 (AcOEt)
3-09	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —N—CH ₃	245.0—247.0 (AcOEt/IPE)
3-10	2	H ₂ NCO— <i>o</i> -C ₆ H ₄ —N—	CH	CH ₃	CH ₃	CH ₃ —C ₆ H ₄ —N—CH ₃	253.0—255.0 (AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
 ETOH = ethanol, ACOET = ethyl acetate, HCl salt = HCl salt, IPE = diisopropyl ether

Table 4^a

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁹	Ar	Metting point (°C) (solvent for crystallization)
4-01	2	H ₂ NCO-	—N—	CH ₃	H	CH ₃		Amorphous ^b
4-02	2	H ₂ NCO-	—N—	CH ₃	H	CH ₃		169.0-171.0(AcOEt/Et ₂ O)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization;
AcOEt = ethyl acetate, Et₂O = diethyl ether

*2: ¹H NMR (200MHz, CDCl₃); δ 2.57-2.75(2H, m), 2.67(3H, s), 3.55(2H, t, J=5.7Hz),
4.01(3H, s), 4.08-4.18(2H, m), 6.70-6.82(1H, m), 7.35(1H, dd, J=2.1, 8.6Hz),
7.49(1H, d, J=2.1Hz), 7.70(1H, s), 8.09(1H, d, J=8.6Hz),

MS (ES, pos.) ; 416(M+1)⁺, 418(M+3)⁺

Table 5*1

Com. No.	Ex. No.	A	E	R ⁴	R ⁹	Ar	Melting point (°C) (solvent for crystallization)
5-01	2	H ₂ NCO-	—N— cyclohexyl	CH ₃	CH ₃		267.0-269.0 (AcOEt)
5-02	2	H ₂ NCO-	—N— cyclohexyl	CH ₃	CH ₃		165.0-167.0 (AcOEt)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization;
AcOEt = ethyl acetate

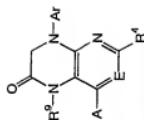


Table 6*1

Com. No.	Ex. No.	A	E	R ⁴	R ⁹	Ar	Melting point (°C) (solvent for crystallization)
6-01	2	H ₂ NCO- C ₆ H ₄ -N-	N	CH ₃	CH ₃	Cl- C ₆ H ₄ -Cl	221.0-223.0 (Et ₂ O)
6-02	2	H ₂ NCO- C ₆ H ₄ -N-	N	CH ₃	CH ₃	Cl- C ₆ H ₄ -Cl	209.0-211.0 (Et ₂ O)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
Et₂O = diethyl ether

Table 7¹

Com. No.	Ex. No.	A	E	R ⁴	R ⁹	Ar	Melting point (°C) (solvent for crystallization)
7-01	2	H ₂ NCO- 	N	CH ₃	CH ₃		266.0-268.0 (AcOEt)
7-02	1	H ₂ NCO- 	CH	CH ₃	CH ₃		231.0-233.0 (AcOEt)
7-03	2	H ₂ NCO- 	N	CH ₃	CH ₃		211.0-213.0 (AcOEt)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization;
AcOEt = ethyl acetate, Et₂O = diethyl ether

Table 8*1

Com. No.	Ex. No.	A	E	R ⁴	Ar	Melting point (°C) (solvent for crystallization)
8-01	2	H ₂ NCO- cyclohexyl-N-	N	CH ₃	Cl cyclohexyl	283.0-285.0 (AcOEt)
8-02	2	H ₂ NCO- cyclohexyl-N-	N	CH ₃	Cl cyclohexyl	186.0-188.0 (AcOEt/IPE)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

Table 9¹

Com. No.	Ex. No.	A	E	R ⁴	Ar	Melting point (°C) (solvent for crystallization)
9-01	2	H ₂ NCO-	—N— cyclohexyl	CH ₃	Cl —C ₆ H ₄ —Cl	191.0-193.0 (AcOEt/IPE)
9-02	2	H ₂ NCO-	—N— cyclohexyl	CH ₃	Cl —C ₆ H ₄ —Cl	217.0-219.0 (AcOEt)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

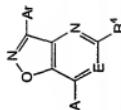


Table 10^{*1}

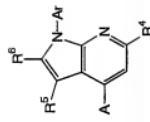
Com. No.	Ex. No.	A	E	R ⁴	R ⁵	R ⁶	Ar	Melting point (°C) (solvent for crystallization)
10-01	2	H ₂ NCO- C ₆ H ₄ -N-	CH ₃	H	H		Cl C ₆ H ₄ -Cl	242.0-244.0 (Et ₂ O)
10-02	2	H ₂ NCO- C ₆ H ₄ -N-	CH ₃	CH ₃	H	H	Cl C ₆ H ₄ -Cl	208.0-210.0 (AcOEt/IPE)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization;
AcOEt = ethyl acetate, Et₂O = diethyl ether, IPE = diisopropyl ether

Table 11^{*1}

Com. No.	Ex. No.	A	E	R ⁴	R ⁵	Ar	Melting point (°C) (solvent for crystallization)
11-01	2	H ₂ NCO— 	N	CH ₃	H		220.0-222.0 (THF/hexane)
11-02	4	H ₂ NCO— 	CH	CH ₃	H		238.0-240.0 (CHCl ₃ /MeOH)
11-03	2	H ₂ NCO— 	N	CH ₃	H		216.0-218.0 (THF/hexane)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization;
MeOH = methanol, THF = tetrahydrofuran

Table 12^a

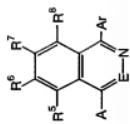
Com. No.	Ex. No.	A	R ⁴	R ⁵	R ⁶	Ar	Melting point (°C) (solvent for crystallization)
12-01	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Cl	Cl	265.0-267.0 (AcOEt)
12-02	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Cl	Cl	273.0-275.0 (AcOEt)
12-03	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Cl	Cl	267.0-269.0 (AcOEt)
12-04	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Br	Br	208.0-210.0 (AcOEt)
12-05	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	CH ₃	Br	170.0-172.0 (AcOEt/1PE)
12-06	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	CH ₃	Br	162.0-164.0 (AcOEt)
12-07	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Br	Br	249.0-251.0 (AcOEt)
12-08	4	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Br	CF ₃	203.0-205.0 (CHCl ₃ /1PE)
12-09	5	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	CH ₃	CH ₃	Cl	Cl	Amorphous ^{*2}

Table 12 (Cont'd)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
ACOEt = ethyl acetate, IPE = diisopropyl ether

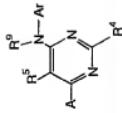
*2: ¹H NMR (200MHz, CDCl₃); δ 2.06(3H, s), 2.40(3H, s), 2.45(3H, br. s), 2.48-2.60(2H, m), 3.21-3.43 (2H, m), 3.86-3.96 (2H, m), 6.54(1H, s), 6.70-6.77(1H, m), 7.29(1H, d, J=8.5Hz), 7.39(1H, dd, J=2.3, 8.5Hz), 7.57(1H, d, J=2.3Hz).

MS (ES, pos); 429 (M+1)⁺, 431 (M+3)⁺

Table 13^{a1}

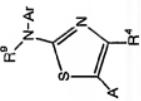
Com.No.	Ex.No.	A	E	R ⁵	R ⁶	R ⁷	R ⁸	Ar	Melting point (°C) (solvent for crystallization)
13-01	2	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	N	H	H	H	H	<i>p</i> -Cl-C ₆ H ₄	294.0-296.0 (THF/CHCl ₃)
13-02	2	H ₂ NCO- <i>p</i> -C ₆ H ₄ -N-	N	H	H	H	H	<i>p</i> -Cl-C ₆ H ₄	133.0-135.0 (AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
ACOEt = ethyl acetate, IPE = diisopropyl ether, THF = tetrahydrofuran

Table 14^{*1}

Com. No.	Ex.No.	A	R ⁴	R ⁵	R ⁹	Ar	Melting point (°C) (solvent for crystallization)
14-01	3	H ₂ NCO-	CH ₃	CH ₃	H		241.0-243.0 (AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
AcOEt = ethyl acetate, IPE = diisopropyl ether

Table 15^{*1}

Com. No.	Ex.No.	A	R ⁴	R ⁹	Ar	Melting point (°C) (solvent for crystallization)
15-01	6	H ₂ NCO-	CH ₃	CH ₂ CH ₃		148.0-150.0 (IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization;
IPE = diisopropyl ether

